REMARKS

Upon entry of the foregoing amendment, claims 20, 22, 23, 25-29, 31, 33, 34, 36 and 40-43 are pending in the application.

Claims 1-19, 21, 24, 30, 32, 35, 37-39 and 44 were previously cancelled. Claims 1-19, 21, 24, 30, 32, 35, 37-39 and 44 are cancelled without prejudice or disclaimer of the cancelled subject matter. Applicants reserve the right to pursue the cancelled subject matter in one or more continuing or divisional applications.

This amendment is not believed to introduce new matter and entry is respectfully requested.

1. PERSONAL INTERVIEW

Applicants wish to thank Examiner Kam for the personal interview held at the Patent and Trademark Office (PTO) with Applicants' representative on May 22, 2007. At the interview, arguments were presented explaining the differences between the claimed invention and the cited prior art. Examiner Kam indicated she would reconsider the rejections in view of Applicants' presented arguments. Applicants' presented arguments form the basis of the current reply to the rejection under 35 U.S.C. § 103, below.

During the interview the Examiner brought a document, French Patent No. 2,778,847 A1 ['847], to the attention of the undersigned. Applicants brought the '847 document to the attention of the Office in an IDS filed at the U.S. Patent and Trademark Office on October 30, 2001, and again with the filing of a Notice of Appeal (January 16, 2002). During prosecution, the '847 document was the basis for at least one rejection under 35 U.S.C. § 103 (see, Office Action mail dated December 31, 2002). The rejection over the '847 document was withdrawn by the Office in the subsequent Office Action. The '847 document is not available as prior art because the publication date of the

document (November 26, 1999) is after the claimed priority date of the instant application (October 15, 1999, based on U.S. Provisional Appl. No. 60/159,739). See, Amendment and Reply filed June 30, 2003 for Applicants' arguments directed to this issue.

2. IDS AND 1449

Applicants note that an IDS and PTO form 1449 were filed February 21, 2007 in the instant application. As evidence of the filing, a photocopy of the date stamped receipt post-card is attached hereto. The Examiner is respectfully requested to consider the documents listed on the PTO 1449 form and return an executed copy of the PTO 1449 form to Applicants with the next communication. For the convenience of the Examiner, an additional copy of the 1449 form is attached hereto. Additional copies of the documents will be provided upon request.

3. WITHDRAWN CLAIM OBJECTIONS

Applicants acknowledge with thanks the withdrawal of the objection to claim 30.

4. REJECTIONS UNDER 35 U.S.C. § 103(a)

Claims 20, 22, 23, 25-29, 31, 34 and 40-43 remain rejected under 35 U.S.C. § 103(a) as unpatentable over Suzuki et al. (U.S. Patent No. 6,197,326, filed October 14, 1998) ["Suzuki"] in view of Igari et al. (U.S. Patent No. 5,416,071, issued on May 16, 1995) ["Igari"]. This rejection is respectfully traversed.

The Office arguments at pages 2-4 are briefly summarized as follows. Suzuki is cited for allegedly teaching a formulation for the treatment of arthropathy comprising microcapsules of a biocompatible high molecular weight substance such PLGA, a homopolymer or copolymer of lactic acid, glycolic acid, caprolactone and others; a drug; administering the microcapsules by injection by suspending the microcapsules in a dispersion medium; use of injection grade water as the dispersion medium; a buffer; an isotonicity; and, a microcapsule dispersing medium containing hyaluronic acid. The Office asserts Suzuki teaches injection of beclomethasone in a dose of 1 mg (citing to

Examples 1-5, Table 1, Test 1) or dexamethasone in a dose of 9 mg (citing to Example 8, Table 2, Test 4). The Office argues that although Suzuki does not specifically indicate the volume used in the injection, Suzuki employs 10 ml in the test release of dexamethasone-containing microcapsules.

The Office argues that Suzuki fails to teach the concentration of hyaluronic acid in the formulation but the deficiency is cured by Igari. Igari is said to teach a pharmaceutical composition suitable for injection comprising erythropoietin or other biological agents such as NGF and hyaluronic acid, a high molecular weight compound known to be biodegradable and injectable at a concentration of 0.01% to 3%.

According to the Office, it would have been obvious to one of ordinary skill in the art to combine the two references to administer a biologically active agent by injecting a formulation comprising hyaluronic acid, a buffer and a microcapsule of a biocompatible polymeric substance and a biologically active agent as taught by Suzuki using the concentration of hyaluronic acid as taught by Igari because the hyaluronic acid at the concentration of 0.01% to 3% would allow the formulation to be easily administered using a small gauge needle such as 26G. Office Action at 3-4.

In response to Applicants' previous arguments, the Office replies (Office Action at 4-5)

> "the arguments are not fully persuasive because Suzuki *et al.* teach injection of beclomethason proprionate (Test 1) in a dose of 1 mg (the drug content is 8.8-10.2% in microcapsules, corresponding to microcapsules in 11.4-9.8 mg for Examples 1-5, Table 1) or dexamethasone in a dose of 9 mg (the drug content is 3.8% in microcapsules, corresponding to microcapsules in 237 mg of Example 8, Table 2; Test 4) into knee joint of rabbits. Although the reference does not specifically indicate the volume used in the injection, it does indicate the use of 10 ml in the test of release of dexamethasone-containing microcapsule samples, thus the concentration of microcapsules in the injection can be 1 or 24 mg/ml (Test 3), which meets the limitation for the concentration of polymeric matrix in the claimed invention, thus the rejection is maintained."

Applicants continue to disagree with the conclusion of the Office. Neither Suzuki or Igari, taken alone or together, teach or suggest a concentration of polymeric matrix which is about 1 mg/mL to about 500 mg/mL of formulation as recited in claims 20 and 22 for at least the following reasons.

Claims 20 and 22 recite, *inter alia*, a formulation comprising a) an injection vehicle, and b) particles comprising two components: a biologically active agent and a biocompatible polymeric matrix. The concentration of the polymeric matrix is about 1mg/mL to about 500 mg/mL of formulation. Contrary to Examiner arguments, it is the concentration of <u>polymeric matrix</u> in the formulation which is claimed and not the concentration of <u>drug</u> in the formulation in claims 20 and 22.

A) SUZUKI DOES NOT FOCUS ON THE POLYMERIC MATRIX OR MEASURE THE CONCENTRATION OF THE POLYMERIC MATRIX IN THE INJECTABLE FORMULATION AS RECITED IN CLAIMS 20 AND 22

One of skill, reading Suzuki, cannot determine the concentration of polymeric matrix in any microparticle because Suzuki does not determine either the polymeric matrix concentration *per se* or the concentration of the additional components (i.e., salts) in the microparticles.

In Suzuki, there is little or no correlation between microparticle size and drug content. See, for example, Table 3, showing that microparticles with a larger average particle size can contain a smaller DXNa (%) concentration than smaller particles (containing a larger % of DXNa). Further, the Suzuki microparticles are formulated in the presence of additional ingredients such as salts (see, for example, column 6, lines 58-61, describing preparation in 27% calcium chloride), liquid paraffin (see, for example, column 8, lines 61-62) and other solvents such as polyvinyl alcohol (see, for example, column 6, line 61), methylene chloride (see, for example, column 6, lines 19-27 and lines 62-67) and acetone (see, for example, column 9, lines 1-3). While the methylene chloride and acetone are allegedly removed from the final microparticles by evaporation (see, for example, column 6, lines 65-67) there is no indication that all the methylene chloride or acetone is removed from the microparticles by evaporation, or, that microparticles

prepared by the method of Example 6 (column 6) have *any* of the methylene chloride removed. Thus, the microcapsules can comprise methylene chloride, as well as other solvents, such as polyvinyl alcohol, employed during the preparation process and trapped within during the encapsulation process.

Because one of skill cannot determine the percentage of the other components present in the microparticles, one cannot assume that a Suzuki microcapsule having a 4.4% drug content must have a 95.6% polymeric matrix content. Therefore, one of skill cannot determine the polymeric matrix content of the microparticles, and hence the concentration of the polymeric matrix in the formulation.

B) SUZUKI FOCUSES ON THE CONCENTRATION OF DRUG RELEASED

Suzuki is directed to methods and compositions for achieving high drug concentration at a target area and which maintain drug efficacy over a long term. The focus of Suzuki is on conditions and compositions for increasing drug release. *See*, for example, the Abstract and the figure legends to Figures 2-12, discussing amounts of drug release under given experimental conditions. ‘

The Examiner relies on Test 3 experimental conditions (“Although the reference does not specifically indicate the volume used in the injection, it does indicate the use of 10 ml in the test of release of dexamethasone-containing microcapsule samples, thus the concentration of microcapsules in the injection can be 1 or 24 mg/ml (Test 3) which meets the limitation for the concentration of polymeric matrix in the claimed invention.”) to meet the claim elements. However, in Test 3, the 10 ml of phosphate buffer was employed to determine release rate of the drug in an experimental system. The composition of Test 3 is not a formulation for injection as recited in claims 20 or 22 because it does not comprise hyaluronic acid.

C) IGARI IS SILENT ON MICROCAPSULE POLYMERIC MATRIX CONCENTRATIONS

Furthermore, contrary to Office arguments, Igari fails to cure the deficiencies of Suzuki. Igari, like Suzuki, focuses on delivery of a drug (see, for example, sustained

release of erythropoietin, column 4, lines 12-20) from a long acting composition comprising hyaluronic acid. Igari is silent on microcapsule components such as a polymeric matrix used in their formulation. Because Igari is silent on the polymeric matrix components of microcapsules, Igari is silent on a formulation comprising a concentration of polymeric matrix of about "1 mg/mL to about 500 mg/mL of formulation" as currently claimed in independent claims 20 and 22.

D) **SUZUKI ALONE OR IN COMBINATION WITH IGARI FAILS TO RENDER OBVIOUS CLAIMS 20, 22 AND CLAIMS DEPENDENT THEREFROM**

As the Office is aware, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Because both Suzuki and Igari are silent on the concentration of polymeric matrix in an injectable formulation as claimed in claims 20 and 22, the combination of documents fails to teach or suggest all the claim limitations. Thus, Suzuki and Igari, alone or together, fail to render obvious independent claims 20 and 22, and claims 23, 25-29, 34 and 40-43, dependent therefrom.

Because the Office has failed to establish a *prima facie* case of obviousness, the rejection is legally deficient. In view of the arguments above, the rejection is believed to be overcome. Reconsideration and withdrawal of the rejection is respectfully requested.

5. CLAIM OBJECTIONS

Applicants note current claims 33 and 36 are objected to as depending from a

rejected base claim. In view of the arguments above, independent claims 20 and 22 are believed to be allowable. Thus, claims 33 and 36, dependent directly or indirectly therefrom, are also allowable. Reconsideration and withdrawal of the objection is respectfully requested.

CONCLUSION

In view of the above remarks, Applicants respectfully request a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

MERCHANT & GOULD P.C.

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